

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVANDIA safely and effectively. See full prescribing information for AVANDIA.

AVANDIA (rosiglitazone maleate) Tablets
Initial U.S. Approval: 1999

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION

See full prescribing information for complete boxed warning.

• Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.

• AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)

• A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with a statistically significant increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of myocardial infarction and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of AVANDIA and ACTOS® (pioglitazone, another thiazolidinedione), but in a separate trial, ACTOS (when compared to placebo) did not show an increased risk of myocardial infarction or death. (5.2)

• Because of the potential increased risk of myocardial infarction, AVANDIA is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com. [See Warnings and Precautions (5.3).]

RECENT MAJOR CHANGES

Boxed Warning	02/2011
Indications and Usage (1)	02/2011
Dosage and Administration (2)	02/2011
Warnings and Precautions, Cardiac Failure (5.1)	02/2011
Warnings and Precautions, Major Adverse Cardiovascular Events (5.2)	02/2011
Warnings and Precautions, Rosiglitazone REMS Program (5.3)	XX/2011
Warnings and Precautions, Fractures (5.8)	02/2011

INDICATIONS AND USAGE

AVANDIA is a thiazolidinedione antidiabetic agent. After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of AVANDIA, this drug is indicated as an adjunct to diet and

exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

- already taking AVANDIA, or
- not already taking AVANDIA and are unable to achieve adequate glycemic control on other diabetes medications, and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) for medical reasons. (1)

Other Important Limitations of Use:

- AVANDIA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. (1)
- Coadministration of AVANDIA and insulin is not recommended. (1, 5.1, 5.2)

DOSAGE AND ADMINISTRATION

- Start at 4 mg daily in single or divided doses; do not exceed 8 mg daily. (2)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2)
- Do not initiate AVANDIA if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.1)

DOSAGE FORMS AND STRENGTHS

Pentagonal, film-coated tablets in the following strengths:

- 2 mg, 4 mg, and 8 mg (3)

CONTRAINDICATIONS

Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4)

WARNINGS AND PRECAUTIONS

- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.1)
- Increased risk of myocardial infarction has been observed in a meta-analysis of 52 clinical trials (incidence rate 0.4% versus 0.3%). (5.2)
- Coadministration of AVANDIA and insulin is not recommended. (1, 5.1, 5.2)
- Dose-related edema (5.4), weight gain (5.5), and anemia (5.9) may occur.
- Macular edema has been reported. (5.7)
- Increased incidence of bone fracture. (5.8)

ADVERSE REACTIONS

Common adverse reactions (>5%) reported in clinical trials without regard to causality were upper respiratory tract infection, injury, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Inhibitors of CYP2C8 (e.g., gemfibrozil) may increase rosiglitazone levels; inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: XX/2011

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION**

- 3 • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in
4 some patients [*see Warnings and Precautions (5.1)*]. After initiation of AVANDIA, and after
5 dose increases, observe patients carefully for signs and symptoms of heart failure (including
6 excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop,
7 the heart failure should be managed according to current standards of care. Furthermore,
8 discontinuation or dose reduction of AVANDIA must be considered.
- 9 • AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of
10 AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated.
11 [*See Contraindications (4) and Warnings and Precautions (5.1)*.]
- 12 • A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of
13 which compared AVANDIA to placebo, showed AVANDIA to be associated with a
14 statistically significant increased risk of myocardial infarction. Three other trials (mean
15 duration 46 months; 14,067 total patients), comparing AVANDIA to some other approved
16 oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of
17 myocardial infarction, and a statistically non-significant decreased risk of death. There have
18 been no clinical trials directly comparing cardiovascular risk of AVANDIA and ACTOS[®]
19 (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared
20 to placebo) did not show an increased risk of myocardial infarction or death. [*See Warnings
21 and Precautions (5.2)*.]
- 22 • Because of the potential increased risk of myocardial infarction, AVANDIA is available only
23 through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines
24 Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-
25 800-AVANDIA or visit www.AVANDIA.com. [*See Warnings and Precautions (5.3)*.]

26 **1 INDICATIONS AND USAGE**

27 After consultation with a healthcare professional who has considered and advised the
28 patient of the risks and benefits of AVANDIA[®], this drug is indicated as an adjunct to diet and
29 exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

- 30 • already taking AVANDIA, or
- 31 • not already taking AVANDIA and are unable to achieve adequate glycemic control on other
32 diabetes medications and, in consultation with their healthcare provider, have decided not to
33 take pioglitazone (ACTOS[®]) for medical reasons.

34 **Other Important Limitations of Use:**

- 35 • Due to its mechanism of action, AVANDIA is active only in the presence of endogenous
36 insulin. Therefore, AVANDIA should not be used in patients with type 1 diabetes mellitus or

37 for the treatment of diabetic ketoacidosis.
38 • The coadministration of AVANDIA and insulin is not recommended [see Warnings and
39 Precautions (5.1)].

40 **2 DOSAGE AND ADMINISTRATION**

41 Prior to prescribing AVANDIA, refer to *Indications and Usage (1)* for appropriate
42 patient selection. Only prescribers enrolled in the AVANDIA-Rosiglitazone Medicines Access
43 Program can prescribe AVANDIA [see Warnings and Precautions (5.3)].

44 AVANDIA may be administered at a starting dose of 4 mg either as a single daily dose or
45 in 2 divided doses. For patients who respond inadequately following 8 to 12 weeks of treatment,
46 as determined by reduction in fasting plasma glucose (FPG), the dose may be increased to 8 mg
47 daily. Increases in the dose of AVANDIA should be accompanied by careful monitoring for
48 adverse events related to fluid retention [see Boxed Warning and Warnings and Precautions
49 (5.1)]. AVANDIA may be taken with or without food.

50 The total daily dose of AVANDIA should not exceed 8 mg.

51 Patients receiving AVANDIA in combination with other hypoglycemic agents may be at
52 risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

53 **2.1 Specific Patient Populations**

54 Renal Impairment: No dosage adjustment is necessary when AVANDIA is used as
55 monotherapy in patients with renal impairment. Since metformin is contraindicated in such
56 patients, concomitant administration of metformin and AVANDIA is also contraindicated in
57 patients with renal impairment.

58 Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment
59 with AVANDIA. Therapy with AVANDIA should not be initiated if the patient exhibits clinical
60 evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit
61 of normal at start of therapy). After initiation of AVANDIA, liver enzymes should be monitored
62 periodically per the clinical judgment of the healthcare professional. [See Warnings and
63 Precautions (5.6) and Clinical Pharmacology (12.3).]

64 Pediatric: Data are insufficient to recommend pediatric use of AVANDIA [see Use in
65 Specific Populations (8.4)].

66 **3 DOSAGE FORMS AND STRENGTHS**

67 Pentagonal film-coated TILTAB[®] tablet contains rosiglitazone as the maleate as follows:

- 68 • 2 mg - pink, debossed with SB on one side and 2 on the other
- 69 • 4 mg - orange, debossed with SB on one side and 4 on the other
- 70 • 8 mg - red-brown, debossed with SB on one side and 8 on the other

71 **4 CONTRAINDICATIONS**

72 Initiation of AVANDIA in patients with established New York Heart Association
73 (NYHA) Class III or IV heart failure is contraindicated [see Boxed Warning].

74 **5 WARNINGS AND PRECAUTIONS**

75 **5.1 Cardiac Failure**

76 AVANDIA, like other thiazolidinediones, alone or in combination with other antidiabetic
77 agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should
78 be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the
79 heart failure should be managed according to current standards of care. Furthermore,
80 discontinuation or dose reduction of rosiglitazone must be considered [*see Boxed Warning*].

81 Patients with congestive heart failure (CHF) NYHA Class I and II treated with
82 AVANDIA have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-
83 controlled echocardiographic trial was conducted in 224 patients with type 2 diabetes mellitus
84 and NYHA Class I or II CHF (ejection fraction $\leq 45\%$) on background antidiabetic and CHF
85 therapy. An independent committee conducted a blinded evaluation of fluid-related events
86 (including congestive heart failure) and cardiovascular hospitalizations according to predefined
87 criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were
88 reported by investigators. Although no treatment difference in change from baseline of ejection
89 fractions was observed, more cardiovascular adverse events were observed following treatment
90 with AVANDIA compared to placebo during the 52-week trial. (See Table 1.)

91

92 Table 1. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart
 93 Failure (NYHA Class I and II) Treated With AVANDIA or Placebo (in Addition to
 94 Background Antidiabetic and CHF Therapy)

Events	AVANDIA	Placebo
	N = 110	N = 114
	n (%)	n (%)
Adjudicated		
Cardiovascular deaths	5 (5%)	4 (4%)
CHF worsening	7 (6%)	4 (4%)
– with overnight hospitalization	5 (5%)	4 (4%)
– without overnight hospitalization	2 (2%)	0 (0%)
New or worsening edema	28 (25%)	10 (9%)
New or worsening dyspnea	29 (26%)	19 (17%)
Increases in CHF medication	36 (33%)	20 (18%)
Cardiovascular hospitalization ^a	21 (19%)	15 (13%)
Investigator-reported, non-adjudicated		
Ischemic adverse events	10 (9%)	5 (4%)
– Myocardial infarction	5 (5%)	2 (2%)
– Angina	6 (5%)	3 (3%)

95 ^a Includes hospitalization for any cardiovascular reason.
 96

97 Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is
 98 contraindicated. AVANDIA is not recommended in patients with symptomatic heart failure. [See
 99 *Boxed Warning.*]

100 Patients experiencing acute coronary syndromes have not been studied in controlled
 101 clinical trials. In view of the potential for development of heart failure in patients having an acute
 102 coronary event, initiation of AVANDIA is not recommended for patients experiencing an acute
 103 coronary event, and discontinuation of AVANDIA during this acute phase should be considered.

104 Patients with NYHA Class III and IV cardiac status (with or without CHF) have not been
 105 studied in controlled clinical trials. AVANDIA is not recommended in patients with NYHA
 106 Class III and IV cardiac status.

107 Congestive Heart Failure During Coadministration of AVANDIA With Insulin: In
 108 trials in which AVANDIA was added to insulin, AVANDIA increased the risk of congestive
 109 heart failure. Coadministration of AVANDIA and insulin is not recommended. [See *Indications*
 110 *and Usage (1) and Warnings and Precautions (5.2).*]

111 In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks

112 and which were included in a meta-analysis¹ [see *Warnings and Precautions (5.2)*], patients with
 113 type 2 diabetes mellitus were randomized to coadministration of AVANDIA and insulin
 114 (N = 1,018) or insulin (N = 815). In these 7 trials, AVANDIA was added to insulin. These trials
 115 included patients with long-standing diabetes (median duration of 12 years) and a high
 116 prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy,
 117 ischemic heart disease, vascular disease, and congestive heart failure. The total number of
 118 patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the AVANDIA
 119 plus insulin and insulin groups, respectively.

120 Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing
 121 AVANDIA to ACTOS: Three observational studies²⁻⁴ in elderly diabetic patients (age 65 years
 122 and older) found that AVANDIA statistically significantly increased the risk of hospitalized
 123 heart failure compared to use of ACTOS. One other observational study⁵ in patients with a mean
 124 age of 54 years, which also included an analysis in a subpopulation of patients >65 years of age,
 125 found no statistically significant increase in emergency department visits or hospitalization for
 126 heart failure in patients treated with AVANDIA compared to ACTOS in the older subgroup.

127 **5.2 Major Adverse Cardiovascular Events**

128 Cardiovascular adverse events have been evaluated in a meta-analysis of 52 clinical
 129 trials, in long-term, prospective, randomized, controlled trials, and in observational studies.

130 Meta-Analysis of Major Adverse Cardiovascular Events in a Group of 52 Clinical
 131 Trials: A meta-analysis was conducted retrospectively to assess cardiovascular adverse events
 132 reported across 52 double-blind, randomized, controlled clinical trials (mean duration 6
 133 months).¹ These trials had been conducted to assess glucose-lowering efficacy in type 2 diabetes.
 134 Prospectively planned adjudication of cardiovascular events did not occur in most of the trials.
 135 Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls.
 136 Placebo-controlled trials included monotherapy trials (monotherapy with AVANDIA versus
 137 placebo monotherapy) and add-on trials (AVANDIA or placebo, added to sulfonylurea,
 138 metformin, or insulin). Active control trials included monotherapy trials (monotherapy with
 139 AVANDIA versus sulfonylurea or metformin monotherapy) and add-on trials (AVANDIA plus
 140 sulfonylurea or AVANDIA plus metformin, versus sulfonylurea plus metformin). A total of
 141 16,995 patients were included (10,039 in treatment groups containing AVANDIA, 6,956 in
 142 comparator groups), with 5,167 patient-years of exposure to AVANDIA and 3,637 patient-years
 143 of exposure to comparator. Cardiovascular events occurred more frequently for patients who
 144 received AVANDIA than for patients who received comparators (see Table 2).
 145

146 **Table 2. Occurrence of Cardiovascular Events in a Meta-Analysis of 52 Clinical Trials**

Event ^a	AVANDIA (Rosiglitazone) (N = 10,039) n (%)	Comparator (N = 6,956) n (%)
MACE (a composite of myocardial	70 (0.7)	39 (0.6)

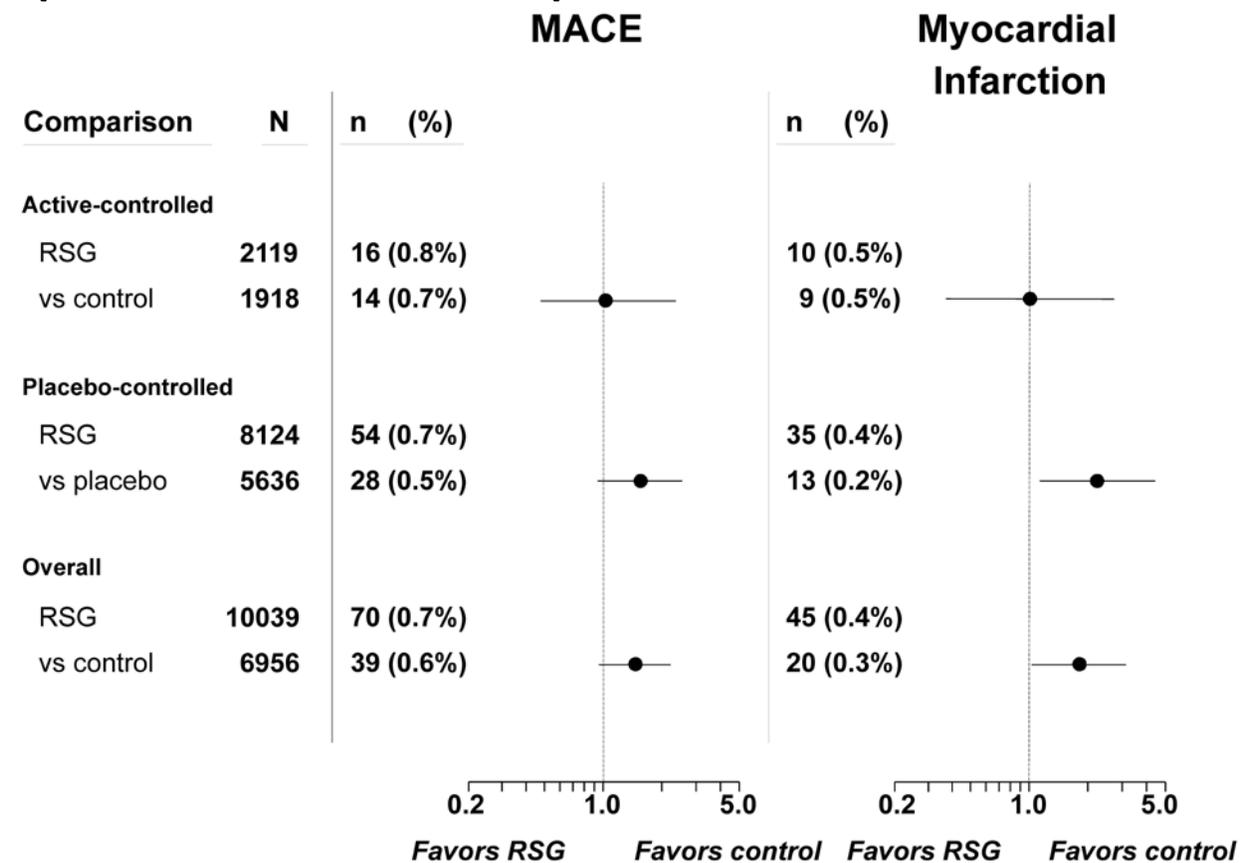
infarction, cardiovascular death, or stroke)		
Myocardial Infarction	45 (0.4)	20 (0.3)
Cardiovascular Death	17 (0.2)	9 (0.1)
Stroke	18 (0.2)	16 (0.2)
All-cause Death	29 (0.3)	17 (0.2)

147 ^a Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial
148 infarction would be counted in 4 event categories (myocardial infarction; myocardial
149 infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).

150
151 In this analysis, a statistically significant increased risk of myocardial infarction with
152 AVANDIA versus pooled comparators was observed. Analyses were performed using a
153 composite of major adverse cardiovascular events (myocardial infarction, stroke, and
154 cardiovascular death), referred to hereafter as MACE. AVANDIA had a statistically non-
155 significant increased risk of MACE compared to the pooled comparators. A statistically
156 significant increased risk of myocardial infarction and statistically non-significant increased risk
157 of MACE with AVANDIA was observed in the placebo-controlled trials. In the active-controlled
158 trials, there was no increased risk of myocardial infarction or MACE. (See Figure 1 and Table 3.)
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Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for MACE and Myocardial Infarction in the Meta-Analysis of 52 Clinical Trials



RSG = rosiglitazone

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Table 3. Occurrence of MACE and Myocardial Infarction in a Meta-Analysis of 52 Clinical Trials by Trial Type

		MACE			Myocardial Infarction	
		N	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Active-Controlled Trials	RSG	2,119	16 (0.8%)	1.05 (0.48, 2.34)	10 (0.5%)	1.00 (0.36, 2.82)
	Control	1,918	14 (0.7%)		9 (0.5%)	
Placebo-Controlled Trials	RSG	8,124	54 (0.7%)	1.53 (0.94, 2.54)	35 (0.4%)	2.23 (1.14, 4.64)
	Placebo	5,636	28 (0.5%)		13 (0.2%)	
Overall	RSG	10,039	70 (0.7%)	1.44 (0.95, 2.20)	45 (0.4%)	1.8 (1.03, 3.25)
	Control	6,956	39 (0.6%)		20 (0.3%)	

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RSG = AVANDIA (rosiglitazone)

Of the placebo-controlled trials in the meta-analysis, 7 trials had patients randomized to AVANDIA plus insulin or insulin. There were more patients in the AVANDIA plus insulin

170 group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths,
 171 and all-cause deaths (see Table 4). The total number of patients with stroke was 5 (0.5%) and 4
 172 (0.5%) in the AVANDIA plus insulin and insulin groups, respectively. The use of AVANDIA in
 173 combination with insulin may increase the risk of myocardial infarction.
 174

175 **Table 4. Occurrence of Cardiovascular Events for AVANDIA in Combination With Insulin**
 176 **in a Meta-Analysis of 52 Clinical Trials**

Event ^a	AVANDIA (Rosiglitazone) (N=1,018) (%)	Insulin (N = 815) (%)	OR (95% CI)
MACE (a composite of myocardial infarction, cardiovascular death, or stroke)	1.3	0.6	2.14 (0.70, 7.83)
Myocardial infarction	0.6	0.1	5.6 (0.67, 262.7)
Cardiovascular death	0.4	0.0	ND, (0.47, ∞)
All cause death	0.6	0.2	2.19 (0.38, 22.61)

177 ND = not defined

178 ^a Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial
 179 infarction would be counted in 4 event categories (myocardial infarction; myocardial
 180 infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).
 181

182 Myocardial Infarction Events in Large, Long-Term, Prospective, Randomized,
 183 Controlled Trials of AVANDIA: Data from 3 large, long-term, prospective, randomized,
 184 controlled clinical trials of AVANDIA were assessed separately from the meta-analysis.⁶⁻⁸ These
 185 3 trials included a total of 14,067 patients (treatment groups containing AVANDIA N = 6,311;
 186 comparator groups N = 7,756), with patient-year exposure of 24,534 patient-years for
 187 AVANDIA and 28,882 patient-years for comparator. Patient populations in the trials included
 188 patients with impaired glucose tolerance, patients with type 2 diabetes who were initiating oral
 189 agent monotherapy, and patients with type 2 diabetes who had failed monotherapy and were
 190 initiating dual oral agent therapy. Duration of follow-up exceeded 3 years in each trial.

191 In each of these trials, there was a statistically non-significant increase in the risk of
 192 myocardial infarction for AVANDIA versus comparator medications.

193 In a long-term, randomized, placebo-controlled, 2x2 factorial trial intended to evaluate
 194 AVANDIA, and separately ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on
 195 progression to overt diabetes in 5,269 subjects with glucose intolerance, the incidence of
 196 myocardial infarction was higher in the subset of subjects who received AVANDIA in
 197 combination with ramipril than among subjects who received ramipril alone but not in the subset
 198 of subjects who received AVANDIA alone compared to placebo.⁶ The higher incidence of
 199 myocardial infarction among subjects who received AVANDIA in combination with ramipril

200 was not confirmed in the two other large (total N = 8,798) long-term, randomized, active-
201 controlled clinical trials conducted in patients with type 2 diabetes, in which 30% and 40% of
202 patients in the two trials reported angiotensin-converting enzyme inhibitor use at baseline.^{7,8}

203 There have been no adequately designed clinical trials directly comparing AVANDIA to
204 ACTOS (pioglitazone) on cardiovascular risks. However, in a long-term, randomized, placebo-
205 controlled cardiovascular outcomes trial comparing ACTOS (pioglitazone) to placebo in patients
206 with type 2 diabetes mellitus and prior macrovascular disease, ACTOS (pioglitazone) was not
207 associated with an increased risk of myocardial infarction or total mortality.⁹

208 The increased risk of myocardial infarction observed in the meta-analysis and large, long-
209 term controlled clinical trials, and the increased risk of MACE observed in the meta-analysis
210 described above, have not translated into a consistent finding of excess mortality from controlled
211 clinical trials or observational studies. Clinical trials have not shown any difference between
212 AVANDIA and comparator medications in overall mortality or CV-related mortality.

213 Mortality in Observational Studies of AVANDIA Compared to ACTOS: Three
214 observational studies in elderly diabetic patients (age 65 years and older) found that AVANDIA
215 statistically significantly increased the risk of all-cause mortality compared to use of ACTOS.²⁻⁴
216 One observational study⁵ in patients with a mean age of 54 years found no difference in all-cause
217 mortality between patients treated with AVANDIA compared to ACTOS and reported similar
218 results in the subpopulation of patients >65 years of age. One additional small, prospective,
219 observational study¹⁰ found no statistically significant differences for CV mortality and all-cause
220 mortality in patients treated with AVANDIA compared to ACTOS.

221 **5.3 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program**

222 Because of the potential increased risk of myocardial infarction, AVANDIA is available
223 only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines
224 Access Program [*see Indications and Usage (1)*]. Both prescribers and patients must enroll in the
225 program to be able to prescribe or receive AVANDIA, respectively. AVANDIA will be available
226 only from specially certified pharmacies participating in the program. As part of the program,
227 prescribers will be educated about the potential increased risk of myocardial infarction and the
228 need to limit the use of AVANDIA to eligible patients. Prescribers will need to discuss with
229 patients the risks and benefits of taking AVANDIA. To enroll, call 1-800-AVANDIA or visit
230 www.AVANDIA.com.

231 **5.4 Edema**

232 AVANDIA should be used with caution in patients with edema. In a clinical trial in
233 healthy volunteers who received 8 mg of AVANDIA once daily for 8 weeks, there was a
234 statistically significant increase in median plasma volume compared to placebo.

235 Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can
236 exacerbate or lead to congestive heart failure, AVANDIA should be used with caution in patients
237 at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure
238 [*see Boxed Warning, Warnings and Precautions (5.1), and Patient Counseling Information*
239 (17)].

240 In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was
 241 reported in patients treated with AVANDIA, and may be dose related. Patients with ongoing
 242 edema were more likely to have adverse events associated with edema if started on combination
 243 therapy with insulin and AVANDIA [see Adverse Reactions (6.1)].

244 5.5 Weight Gain

245 Dose-related weight gain was seen with AVANDIA alone and in combination with other
 246 hypoglycemic agents (Table 5). The mechanism of weight gain is unclear but probably involves
 247 a combination of fluid retention and fat accumulation.

248 In postmarketing experience, there have been reports of unusually rapid increases in
 249 weight and increases in excess of that generally observed in clinical trials. Patients who
 250 experience such increases should be assessed for fluid accumulation and volume-related events
 251 such as excessive edema and congestive heart failure [see Boxed Warning].

252

253 Table 5. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials

		Control Group		AVANDIA 4 mg	AVANDIA 8 mg
Monotherapy	Duration		Median (25 th , 75 th percentile)	Median (25 th , 75 th percentile)	Median (25 th , 75 th percentile)
	26 weeks	placebo	-0.9 (-2.8, 0.9) N = 210	1.0 (-0.9, 3.6) N = 436	3.1 (1.1, 5.8) N = 439
	52 weeks	sulfonylurea	2.0 (0, 4.0) N = 173	2.0 (-0.6, 4.0) N = 150	2.6 (0, 5.3) N = 157
Combination therapy					
Sulfonylurea	24-26 weeks	sulfonylurea	0 (-1.0, 1.3) N = 1,155	2.2 (0.5, 4.0) N = 613	3.5 (1.4, 5.9) N = 841
Metformin	26 weeks	metformin	-1.4 (-3.2, 0.2) N = 175	0.8 (-1.0, 2.6) N = 100	2.1 (0, 4.3) N = 184
Insulin	26 weeks	insulin	0.9 (-0.5, 2.7) N = 162	4.1 (1.4, 6.3) N = 164	5.4 (3.4, 7.3) N = 150
Sulfonylurea + metformin	26 weeks	sulfonylurea + metformin	0.2 (-1.2, 1.6) N = 272	2.5 (0.8, 4.6) N = 275	4.5 (2.4, 7.3) N = 276

254
 255 In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed
 256 with type 2 diabetes not previously treated with antidiabetic medication [see Clinical Studies
 257 (14.1)], the median weight change (25th, 75th percentiles) from baseline at 4 years was 3.5 kg
 258 (0.0, 8.1) for AVANDIA, 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

259 In a 24-week trial in pediatric patients aged 10 to 17 years treated with AVANDIA 4 to
 260 8 mg daily, a median weight gain of 2.8 kg (25th, 75th percentiles: 0.0, 5.8) was reported.

261 **5.6 Hepatic Effects**

262 Liver enzymes should be measured prior to the initiation of therapy with AVANDIA in
263 all patients and periodically thereafter per the clinical judgment of the healthcare professional.
264 Therapy with AVANDIA should not be initiated in patients with increased baseline liver enzyme
265 levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT
266 levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDIA should be
267 evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of,
268 therapy with AVANDIA in patients with mild liver enzyme elevations should proceed with
269 caution and include close clinical follow-up, including liver enzyme monitoring, to determine if
270 the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the
271 upper limit of normal in patients on therapy with AVANDIA, liver enzyme levels should be
272 rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with
273 AVANDIA should be discontinued.

274 If any patient develops symptoms suggesting hepatic dysfunction, which may include
275 unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver
276 enzymes should be checked. The decision whether to continue the patient on therapy with
277 AVANDIA should be guided by clinical judgment pending laboratory evaluations. If jaundice is
278 observed, drug therapy should be discontinued. [*See Adverse Reactions (6.2, 6.3).*]

279 **5.7 Macular Edema**

280 Macular edema has been reported in postmarketing experience in some diabetic patients
281 who were taking AVANDIA or another thiazolidinedione. Some patients presented with blurred
282 vision or decreased visual acuity, but some patients appear to have been diagnosed on routine
283 ophthalmologic examination. Most patients had peripheral edema at the time macular edema was
284 diagnosed. Some patients had improvement in their macular edema after discontinuation of their
285 thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist,
286 per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who
287 reports any kind of visual symptom should be promptly referred to an ophthalmologist,
288 regardless of the patient's underlying medications or other physical findings. [*See Adverse*
289 *Reactions (6.1).*]

290 **5.8 Fractures**

291 In a 4- to 6-year comparative trial (ADOPT) of glycemic control with monotherapy in
292 drug-naïve patients recently diagnosed with type 2 diabetes mellitus, an increased incidence of
293 bone fracture was noted in female patients taking AVANDIA. Over the 4- to 6-year period, the
294 incidence of bone fracture in females was 9.3% (60/645) for AVANDIA versus 3.5% (21/605)
295 for glyburide and 5.1% (30/590) for metformin. This increased incidence was noted after the first
296 year of treatment and persisted during the course of the trial. The majority of the fractures in the
297 women who received AVANDIA occurred in the upper arm, hand, and foot. These sites of
298 fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip
299 or spine). Other trials suggest that this risk may also apply to men, although the risk of fracture
300 among women appears higher than that among men. The risk of fracture should be considered in

301 the care of patients treated with AVANDIA, and attention given to assessing and maintaining
302 bone health according to current standards of care.

303 **5.9 Hematologic Effects**

304 Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult
305 patients treated with AVANDIA [*see Adverse Reactions (6.2)*]. The observed changes may be
306 related to the increased plasma volume observed with treatment with AVANDIA.

307 **5.10 Diabetes and Blood Glucose Control**

308 Patients receiving AVANDIA in combination with other hypoglycemic agents may be at
309 risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

310 Periodic fasting blood glucose and HbA1c measurements should be performed to monitor
311 therapeutic response.

312 **5.11 Ovulation**

313 Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some
314 premenopausal anovulatory women. As a result, these patients may be at an increased risk for
315 pregnancy while taking AVANDIA [*see Use in Specific Populations (8.1)*]. Thus, adequate
316 contraception in premenopausal women should be recommended. This possible effect has not
317 been specifically investigated in clinical trials; therefore, the frequency of this occurrence is not
318 known.

319 Although hormonal imbalance has been seen in preclinical studies [*see Nonclinical*
320 *Toxicology (13.1)*], the clinical significance of this finding is not known. If unexpected menstrual
321 dysfunction occurs, the benefits of continued therapy with AVANDIA should be reviewed.

322 **6 ADVERSE REACTIONS**

323 **6.1 Clinical Trial Experience**

324 Adult: In clinical trials, approximately 9,900 patients with type 2 diabetes have been
325 treated with AVANDIA.

326 *Short-Term Trials of AVANDIA as Monotherapy and in Combination With Other*
327 *Hypoglycemic Agents*: The incidence and types of adverse events reported in short-term
328 clinical trials of AVANDIA as monotherapy are shown in Table 6.
329

330 Table 6. Adverse Events ($\geq 5\%$ in Any Treatment Group) Reported by Patients in Short-
 331 Term^a Double-Blind Clinical Trials With AVANDIA as Monotherapy

Preferred Term	AVANDIA Monotherapy	Placebo	Metformin	Sulfonylureas ^b
	N = 2,526	N = 601	N = 225	N = 626
	%	%	%	%
Upper respiratory tract infection	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
Fatigue	3.6	5.0	4.0	1.9
Sinusitis	3.2	4.5	5.3	3.0
Diarrhea	2.3	3.3	15.6	3.0
Hypoglycemia	0.6	0.2	1.3	5.9

332 ^a Short-term trials ranged from 8 weeks to 1 year.

333 ^b Includes patients receiving glyburide (N = 514), gliclazide (N = 91), or glipizide (N = 21).
 334

335 Overall, the types of adverse reactions without regard to causality reported when
 336 AVANDIA was used in combination with a sulfonylurea or metformin were similar to those
 337 during monotherapy with AVANDIA.

338 Events of anemia and edema tended to be reported more frequently at higher doses, and
 339 were generally mild to moderate in severity and usually did not require discontinuation of
 340 treatment with AVANDIA.

341 In double-blind trials, anemia was reported in 1.9% of patients receiving AVANDIA as
 342 monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas, and 2.2% on metformin.
 343 Reports of anemia were greater in patients treated with a combination of AVANDIA and
 344 metformin (7.1%) and with a combination of AVANDIA and a sulfonylurea plus metformin
 345 (6.7%) compared to monotherapy with AVANDIA or in combination with a sulfonylurea
 346 (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin
 347 combination clinical trials may have contributed to the higher reporting rate of anemia in these
 348 trials [see *Adverse Reactions* (6.2)].

349 In clinical trials, edema was reported in 4.8% of patients receiving AVANDIA as
 350 monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. The
 351 reporting rate of edema was higher for AVANDIA 8 mg in sulfonylurea combinations (12.4%)
 352 compared to other combinations, with the exception of insulin. Edema was reported in 14.7% of
 353 patients receiving AVANDIA in the insulin combination trials compared to 5.4% on insulin
 354 alone. Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1%
 355 for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with AVANDIA [see

356 *Boxed Warning and Warnings and Precautions (5.1)*]. The use of AVANDIA in combination
 357 with insulin may increase the risk of myocardial infarction [*see Warnings and Precautions*
 358 (5.2)].

359 In controlled combination therapy trials with sulfonylureas, mild to moderate
 360 hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were
 361 withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be
 362 severe (<1%). Hypoglycemia was the most frequently reported adverse event in the fixed-dose
 363 insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for
 364 AVANDIA plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by
 365 capillary blood glucose concentration ≤ 50 mg/dL, were 6% for insulin alone and 12% (4 mg) and
 366 14% (8 mg) for insulin in combination with AVANDIA. [*See Warnings and Precautions (5.10).*]

367 *Long-Term Trial of AVANDIA as Monotherapy*: A 4- to 6-year trial (ADOPT)
 368 compared the use of AVANDIA (n = 1,456), glyburide (n = 1,441), and metformin (n = 1,454)
 369 as monotherapy in patients recently diagnosed with type 2 diabetes who were not previously
 370 treated with antidiabetic medication. Table 7 presents adverse reactions without regard to
 371 causality; rates are expressed per 100 patient-years (PY) exposure to account for the differences
 372 in exposure to trial medication across the 3 treatment groups.

373 In ADOPT, fractures were reported in a greater number of women treated with
 374 AVANDIA (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years) or
 375 metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who
 376 received rosiglitazone were reported in the upper arm, hand, and foot. [*See Warnings and*
 377 *Precautions (5.8).*] The observed incidence of fractures for male patients was similar among the
 378 3 treatment groups.

379
 380 Table 7. On-Therapy Adverse Events (≥ 5 Events/100 Patient-Years [PY]) in Any
 381 Treatment Group Reported in a 4- to 6-Year Clinical Trial of AVANDIA as Monotherapy
 382 (ADOPT)

	AVANDIA N = 1,456 PY = 4,954	Glyburide N = 1,441 PY = 4,244	Metformin N = 1,454 PY = 4,906
Nasopharyngitis	6.3	6.9	6.6
Back pain	5.1	4.9	5.3
Arthralgia	5.0	4.8	4.2
Hypertension	4.4	6.0	6.1
Upper respiratory tract infection	4.3	5.0	4.7
Hypoglycemia	2.9	13.0	3.4
Diarrhea	2.5	3.2	6.8

383
 384 Pediatric: AVANDIA has been evaluated for safety in a single, active-controlled trial of
 385 pediatric patients with type 2 diabetes in which 99 were treated with AVANDIA and 101 were

386 treated with metformin. The most common adverse reactions (>10%) without regard to causality
387 for either AVANDIA or metformin were headache (17% versus 14%), nausea (4% versus 11%),
388 nasopharyngitis (3% versus 12%), and diarrhea (1% versus 13%). In this trial, one case of
389 diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in
390 the rosiglitazone group who had FPG of ~300 mg/dL, 2+ ketonuria, and an elevated anion gap.

391 **6.2 Laboratory Abnormalities**

392 Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related
393 fashion in adult patients treated with AVANDIA (mean decreases in individual trials as much as
394 1.0 g/dL hemoglobin and as much as 3.3% hematocrit). The changes occurred primarily during
395 the first 3 months following initiation of therapy with AVANDIA or following a dose increase in
396 AVANDIA. The time course and magnitude of decreases were similar in patients treated with a
397 combination of AVANDIA and other hypoglycemic agents or monotherapy with AVANDIA.
398 Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin
399 combination trials and may have contributed to the higher reporting rate of anemia. In a single
400 trial in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL
401 and 0.95%, respectively) were reported. Small decreases in hemoglobin and hematocrit have also
402 been reported in pediatric patients treated with AVANDIA. White blood cell counts also
403 decreased slightly in adult patients treated with AVANDIA. Decreases in hematologic
404 parameters may be related to increased plasma volume observed with treatment with
405 AVANDIA.

406 Lipids: Changes in serum lipids have been observed following treatment with
407 AVANDIA in adults [*see Clinical Pharmacology (12.2)*]. Small changes in serum lipid
408 parameters were reported in children treated with AVANDIA for 24 weeks.

409 Serum Transaminase Levels: In pre-approval clinical trials in 4,598 patients treated
410 with AVANDIA (3,600 patient-years of exposure) and in a long-term 4- to 6-year trial in 1,456
411 patients treated with AVANDIA (4,954 patient-years exposure), there was no evidence of
412 drug-induced hepatotoxicity.

413 In pre-approval controlled trials, 0.2% of patients treated with AVANDIA had elevations
414 in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active
415 comparators. The ALT elevations in patients treated with AVANDIA were reversible.
416 Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA compared with 0.9%
417 treated with placebo and 1% in patients treated with active comparators. In pre-approval clinical
418 trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. [*See*
419 *Warnings and Precautions (5.6).*]

420 In the 4- to 6-year ADOPT trial, patients treated with AVANDIA (4,954 patient-years
421 exposure), glyburide (4,244 patient-years exposure), or metformin (4,906 patient-years
422 exposure), as monotherapy, had the same rate of ALT increase to >3X upper limit of normal
423 (0.3 per 100 patient-years exposure).

424 **6.3 Postmarketing Experience**

425 In addition to adverse reactions reported from clinical trials, the events described below

426 have been identified during post-approval use of AVANDIA. Because these events are reported
427 voluntarily from a population of unknown size, it is not possible to reliably estimate their
428 frequency or to always establish a causal relationship to drug exposure.

429 In patients receiving thiazolidinedione therapy, serious adverse events with or without a
430 fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary
431 edema, and pleural effusions) have been reported [*see Boxed Warning and Warnings and*
432 *Precautions (5.1)*].

433 There are postmarketing reports with AVANDIA of hepatitis, hepatic enzyme elevations
434 to 3 or more times the upper limit of normal, and hepatic failure with and without fatal outcome,
435 although causality has not been established.

436 There are postmarketing reports with AVANDIA of rash, pruritus, urticaria, angioedema,
437 anaphylactic reaction, Stevens-Johnson syndrome, and new onset or worsening diabetic macular
438 edema with decreased visual acuity [*see Warnings and Precautions (5.7)*].

439 **7 DRUG INTERACTIONS**

440 **7.1 CYP2C8 Inhibitors and Inducers**

441 An inhibitor of CYP2C8 (e.g., gemfibrozil) may increase the AUC of rosiglitazone and
442 an inducer of CYP2C8 (e.g., rifampin) may decrease the AUC of rosiglitazone. Therefore, if an
443 inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone,
444 changes in diabetes treatment may be needed based upon clinical response. [*See Clinical*
445 *Pharmacology (12.4)*].

446 **8 USE IN SPECIFIC POPULATIONS**

447 **8.1 Pregnancy**

448 Pregnancy Category C.

449 All pregnancies have a background risk of birth defects, loss, or other adverse outcome
450 regardless of drug exposure. This background risk is increased in pregnancies complicated by
451 hyperglycemia and may be decreased with good metabolic control. It is essential for patients
452 with diabetes or history of gestational diabetes to maintain good metabolic control before
453 conception and throughout pregnancy. Careful monitoring of glucose control is essential in such
454 patients. Most experts recommend that insulin monotherapy be used during pregnancy to
455 maintain blood glucose levels as close to normal as possible.

456 Human Data: Rosiglitazone has been reported to cross the human placenta and be
457 detectable in fetal tissue. The clinical significance of these findings is unknown. There are no
458 adequate and well-controlled trials in pregnant women. AVANDIA should not be used during
459 pregnancy.

460 Animal Studies: There was no effect on implantation or the embryo with rosiglitazone
461 treatment during early pregnancy in rats, but treatment during mid-late gestation was associated
462 with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed
463 at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human
464 AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused

465 placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation
466 reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible
467 after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was
468 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately
469 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced
470 the number of uterine implantations and live offspring when juvenile female rats were treated at
471 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human
472 AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day
473 (approximately 4 times human AUC at the maximum recommended daily dose). There was no
474 effect on pre- or post-natal survival or growth.

475 **8.2 Labor and Delivery**

476 The effect of rosiglitazone on labor and delivery in humans is not known.

477 **8.3 Nursing Mothers**

478 Drug-related material was detected in milk from lactating rats. It is not known whether
479 AVANDIA is excreted in human milk. Because many drugs are excreted in human milk,
480 AVANDIA should not be administered to a nursing woman.

481 **8.4 Pediatric Use**

482 After placebo run-in including diet counseling, children with type 2 diabetes mellitus,
483 aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m^2 , were
484 randomized to treatment with 2 mg twice daily of AVANDIA (n = 99) or 500 mg twice daily of
485 metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, FPG decreased in
486 patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior
487 medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of
488 treatment, 49% of patients treated with AVANDIA and 55% of metformin-treated patients had
489 their dose doubled if FPG >126 mg/dL. For the overall intent-to-treat population, at week 24, the
490 mean change from baseline in HbA1c was -0.14% with AVANDIA and -0.49% with metformin.
491 There was an insufficient number of patients in this trial to establish statistically whether these
492 observed mean treatment effects were similar or different. Treatment effects differed for patients
493 naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic
494 therapy (Table 8).

495

496 Table 8. Week 24 FPG and HbA1c Change From Baseline Last-Observation-Carried
 497 Forward in Children With Baseline HbA1c >6.5%

	Naïve Patients		Previously-Treated Patients	
	Metformin	Rosiglitazone	Metformin	Rosiglitazone
	N = 40	N = 45	N = 43	N = 32
FPG (mg/dL)				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted treatment difference ^a (rosiglitazone–metformin) ^b (95% CI)		8 (-15, 30)		21 (-9, 51)
% of patients with ≥30 mg/dL decrease from baseline	43%	27%	44%	28%
HbA1c (%)				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted treatment difference ^a (rosiglitazone–metformin) ^b (95% CI)		0.2 (-0.6, 0.9)		0.5 (-0.2, 1.3)
% of patients with ≥0.7% decrease from baseline	63%	52%	54%	31%

498 ^a Change from baseline means are least squares means adjusting for baseline HbA1c, gender,
 499 and region.

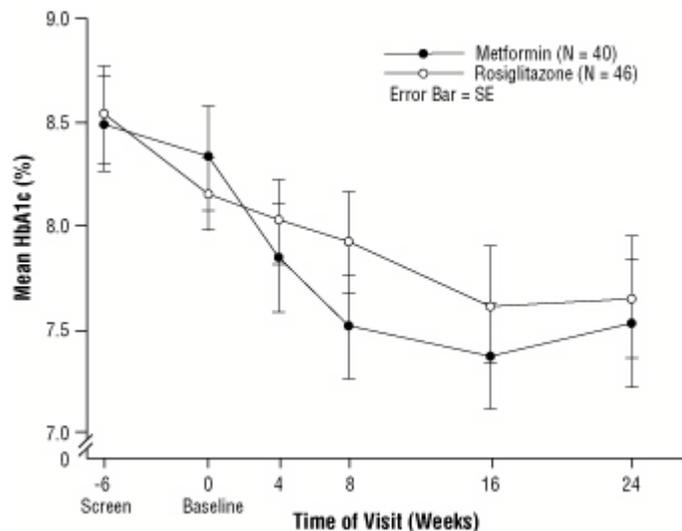
500 ^b Positive values for the difference favor metformin.

501
 502 Treatment differences depended on baseline BMI or weight such that the effects of
 503 AVANDIA and metformin appeared more closely comparable among heavier patients. The
 504 median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin [see *Warnings and*
 505 *Precautions (5.5)*]. Fifty-four percent of patients treated with rosiglitazone and 32% of patients
 506 treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of
 507 patients treated with metformin gained ≥5 kg on trial.

508 Adverse events observed in this trial are described in *Adverse Reactions (6.1)*.

509

510 Figure 2. Mean HbA1c Over Time in a 24-Week Trial of AVANDIA and Metformin in
511 Pediatric Patients — Drug-Naïve Subgroup



512
513

514 8.5 Geriatric Use

515 Results of the population pharmacokinetic analysis showed that age does not significantly
516 affect the pharmacokinetics of rosiglitazone [see *Clinical Pharmacology (12.3)*]. Therefore, no
517 dosage adjustments are required for the elderly. In controlled clinical trials, no overall
518 differences in safety and effectiveness between older (≥ 65 years) and younger (< 65 years)
519 patients were observed.

520 10 OVERDOSAGE

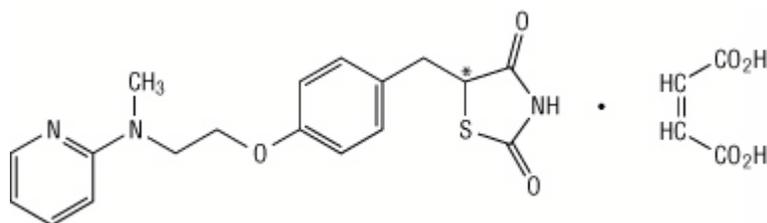
521 Limited data are available with regard to overdosage in humans. In clinical trials in
522 volunteers, AVANDIA has been administered at single oral doses of up to 20 mg and was
523 well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated
524 as dictated by the patient's clinical status.

525 11 DESCRIPTION

526 AVANDIA (rosiglitazone maleate) is an oral antidiabetic agent which acts primarily by
527 increasing insulin sensitivity. AVANDIA improves glycemic control while reducing circulating
528 insulin levels.

529 Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the
530 biguanides, or the alpha-glucosidase inhibitors.

531 Chemically, rosiglitazone maleate is (\pm)-5-[[4-[2-(methyl-2-
532 pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate (1:1) with a
533 molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is
534 present as a racemate. Due to rapid interconversion, the enantiomers are functionally
535 indistinguishable. The structural formula of rosiglitazone maleate is:



536
537 The molecular formula is $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$. Rosiglitazone maleate is a white to
538 off-white solid with a melting point range of 122° to $123^\circ C$. The pKa values of rosiglitazone
539 maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH
540 of 2.3; solubility decreases with increasing pH in the physiological range.

541 Each pentagonal film-coated TILTAB tablet contains rosiglitazone maleate equivalent to
542 rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are:
543 Hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose,
544 polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of
545 the following: Synthetic red and yellow iron oxides and talc.

546 12 CLINICAL PHARMACOLOGY

547 12.1 Mechanism of Action

548 Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves
549 glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent
550 agonist for the peroxisome proliferator-activated receptor-gamma ($PPAR\gamma$). In humans, $PPAR$
551 receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle,
552 and liver. Activation of $PPAR\gamma$ nuclear receptors regulates the transcription of insulin-responsive
553 genes involved in the control of glucose production, transport, and utilization. In addition,
554 $PPAR\gamma$ -responsive genes also participate in the regulation of fatty acid metabolism.

555 Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes.
556 The antidiabetic activity of rosiglitazone has been demonstrated in animal models of type 2
557 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin
558 resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces
559 hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

560 In animal models, the antidiabetic activity of rosiglitazone was shown to be mediated by
561 increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. Pharmacological
562 studies in animal models indicate that rosiglitazone inhibits hepatic gluconeogenesis. The
563 expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue.
564 Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired
565 glucose tolerance.

566 12.2 Pharmacodynamics

567 Patients with lipid abnormalities were not excluded from clinical trials of AVANDIA. In
568 all 26-week controlled trials, across the recommended dose range, AVANDIA as monotherapy
569 was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty
570 acids. These changes were statistically significantly different from placebo or glyburide controls

571 (Table 9).

572 Increases in LDL occurred primarily during the first 1 to 2 months of therapy with
573 AVANDIA and LDL levels remained elevated above baseline throughout the trials. In contrast,
574 HDL continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of
575 therapy and then appeared to decrease over time. Because of the temporal nature of lipid
576 changes, the 52-week glyburide-controlled trial is most pertinent to assess long-term effects on
577 lipids. At baseline, week 26, and week 52, mean LDL/HDL ratios were 3.1, 3.2, and 3.0,
578 respectively, for AVANDIA 4 mg twice daily. The corresponding values for glyburide were 3.2,
579 3.1, and 2.9. The differences in change from baseline between AVANDIA and glyburide at
580 week 52 were statistically significant.

581 The pattern of LDL and HDL changes following therapy with AVANDIA in combination
582 with other hypoglycemic agents were generally similar to those seen with AVANDIA in
583 monotherapy.

584 The changes in triglycerides during therapy with AVANDIA were variable and were
585 generally not statistically different from placebo or glyburide controls.

586

587 Table 9. Summary of Mean Lipid Changes in 26-Week Placebo-Controlled and 52-Week
588 Glyburide-Controlled Monotherapy Trials

	Placebo-Controlled Trials			Glyburide-Controlled Trial			
	Week 26			Week 26 and Week 52			
	Placebo	AVANDIA		Glyburide Titration		AVANDIA 8 mg	
		4 mg daily ^a	8 mg daily ^a	Wk 26	Wk 52	Wk 26	Wk 52
Free fatty acids							
N	207	428	436	181	168	166	145
Baseline (mean)	18.1	17.5	17.9	26.4	26.4	26.9	26.6
% Change from baseline (mean)	+0.2%	-7.8%	-14.7%	-2.4%	-4.7%	-20.8%	-21.5%
LDL							
N	190	400	374	175	160	161	133
Baseline (mean)	123.7	126.8	125.3	142.7	141.9	142.1	142.1
% Change from baseline (mean)	+4.8%	+14.1%	+18.6%	-0.9%	-0.5%	+11.9%	+12.1%
HDL							
N	208	429	436	184	170	170	145
Baseline (mean)	44.1	44.4	43.0	47.2	47.7	48.4	48.3
% Change from baseline (mean)	+8.0%	+11.4%	+14.2%	+4.3%	+8.7%	+14.0%	+18.5%

589 ^a Once daily and twice daily dosing groups were combined.

590

591 **12.3 Pharmacokinetics**

592 Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of
593 rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (Table 10).
594 The elimination half-life is 3 to 4 hours and is independent of dose.

595
596 Table 10. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral
597 Doses (N = 32)

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
AUC _{0-inf} [ng•hr/mL]	358 (112)	733 (184)	2,971 (730)	2,890 (795)
C _{max} [ng/mL]	76 (13)	156 (42)	598 (117)	432 (92)
Half-life [hr]	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F ^a [L/hr]	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)

598 ^a CL/F = Oral clearance.

599
600 **Absorption:** The absolute bioavailability of rosiglitazone is 99%. Peak plasma
601 concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food
602 resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease
603 in C_{max} and a delay in T_{max} (1.75 hours). These changes are not likely to be clinically significant;
604 therefore, AVANDIA may be administered with or without food.

605 **Distribution:** The mean (CV%) oral volume of distribution (V_{ss}/F) of rosiglitazone is
606 approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone
607 is approximately 99.8% bound to plasma proteins, primarily albumin.

608 **Metabolism:** Rosiglitazone is extensively metabolized with no unchanged drug excreted
609 in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed
610 by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably
611 less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing
612 activity of rosiglitazone.

613 In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome
614 P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

615 **Excretion:** Following oral or intravenous administration of [¹⁴C]rosiglitazone maleate,
616 approximately 64% and 23% of the dose was eliminated in the urine and in the feces,
617 respectively. The plasma half-life of [¹⁴C]related material ranged from 103 to 158 hours.

618 **Population Pharmacokinetics in Patients With Type 2 Diabetes:** Population
619 pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with
620 type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not

621 influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral
622 steady-state volume of distribution (V_{ss}/F) were shown to increase with increases in body
623 weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted
624 CL/F and V_{ss}/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally,
625 rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about
626 15%) in female patients.

627 **Special Populations: Geriatric:** Results of the population pharmacokinetic analysis
628 (n = 716 <65 years; n = 331 ≥65 years) showed that age does not significantly affect the
629 pharmacokinetics of rosiglitazone.

630 **Gender:** Results of the population pharmacokinetics analysis showed that the mean oral
631 clearance of rosiglitazone in female patients (n = 405) was approximately 6% lower compared to
632 male patients of the same body weight (n = 642).

633 As monotherapy and in combination with metformin, AVANDIA improved glycemic
634 control in both males and females. In metformin combination trials, efficacy was demonstrated
635 with no gender differences in glycemic response.

636 In monotherapy trials, a greater therapeutic response was observed in females; however,
637 in more obese patients, gender differences were less evident. For a given body mass index
638 (BMI), females tend to have a greater fat mass than males. Since the molecular target PPAR_γ is
639 expressed in adipose tissues, this differentiating characteristic may account, at least in part, for
640 the greater response to AVANDIA in females. Since therapy should be individualized, no dose
641 adjustments are necessary based on gender alone.

642 **Hepatic Impairment:** Unbound oral clearance of rosiglitazone was significantly lower in
643 patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy
644 subjects. As a result, unbound C_{max} and AUC_{0-inf} were increased 2- and 3-fold, respectively.
645 Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease,
646 compared to healthy subjects.

647 Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence
648 of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of
649 normal) at baseline [see *Warnings and Precautions* (5.6)].

650 **Pediatric:** Pharmacokinetic parameters of rosiglitazone in pediatric patients were
651 established using a population pharmacokinetic analysis with sparse data from 96 pediatric
652 patients in a single pediatric clinical trial including 33 males and 63 females with ages ranging
653 from 10 to 17 years (weights ranging from 35 to 178.3 kg). Population mean CL/F and V/F of
654 rosiglitazone were 3.15 L/hr and 13.5 L, respectively. These estimates of CL/F and V/F were
655 consistent with the typical parameter estimates from a prior adult population analysis.

656 **Renal Impairment:** There are no clinically relevant differences in the pharmacokinetics
657 of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent
658 patients compared to subjects with normal renal function. No dosage adjustment is therefore
659 required in such patients receiving AVANDIA. Since metformin is contraindicated in patients
660 with renal impairment, coadministration of metformin with AVANDIA is contraindicated in

661 these patients.

662 **Race:** Results of a population pharmacokinetic analysis including subjects of Caucasian,
663 black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of
664 rosiglitazone.

665 **12.4 Drug-Drug Interactions**

666 **Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P450:** In vitro drug
667 metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at
668 clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly
669 metabolized by CYP2C8, and to a lesser extent, 2C9. AVANDIA (4 mg twice daily) was shown
670 to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral
671 contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by
672 CYP3A4.

673 **Gemfibrozil:** Concomitant administration of gemfibrozil (600 mg twice daily), an
674 inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone
675 AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given
676 the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of
677 rosiglitazone may be needed when gemfibrozil is introduced [*see Drug Interactions (7.1)*].

678 **Rifampin:** Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6
679 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of
680 rosiglitazone (8 mg) alone [*see Drug Interactions (7.1)*].¹¹

681 **Glyburide:** AVANDIA (2 mg twice daily) taken concomitantly with glyburide (3.75 to
682 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations
683 in diabetic patients stabilized on glyburide therapy. Repeat doses of AVANDIA (8 mg once
684 daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and
685 C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased
686 following coadministration of AVANDIA.

687 **Glimepiride:** Single oral doses of glimepiride in 14 healthy adult subjects had no
688 clinically significant effect on the steady-state pharmacokinetics of AVANDIA. No clinically
689 significant reductions in glimepiride AUC and C_{max} were observed after repeat doses of
690 AVANDIA (8 mg once daily) for 8 days in healthy adult subjects.

691 **Metformin:** Concurrent administration of AVANDIA (2 mg twice daily) and metformin
692 (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state
693 pharmacokinetics of either metformin or rosiglitazone.

694 **Acarbose:** Coadministration of acarbose (100 mg three times daily) for 7 days in healthy
695 volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of
696 AVANDIA.

697 **Digoxin:** Repeat oral dosing of AVANDIA (8 mg once daily) for 14 days did not alter the
698 steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

699 **Warfarin:** Repeat dosing with AVANDIA had no clinically relevant effect on the
700 steady-state pharmacokinetics of warfarin enantiomers.

701 Ethanol: A single administration of a moderate amount of alcohol did not increase the
702 risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with AVANDIA.

703 Ranitidine: Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the
704 pharmacokinetics of either single oral or intravenous doses of rosiglitazone in healthy volunteers.
705 These results suggest that the absorption of oral rosiglitazone is not altered in conditions
706 accompanied by increases in gastrointestinal pH.

707 **13 NONCLINICAL TOXICOLOGY**

708 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

709 Carcinogenesis: A 2-year carcinogenicity study was conducted in Charles River CD-1
710 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately
711 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats
712 were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose
713 equivalent to approximately 10 and 20 times human AUC at the maximum recommended human
714 daily dose for male and female rats, respectively).

715 Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of
716 adipose hyperplasia in the mouse at doses ≥ 1.5 mg/kg/day (approximately 2 times human AUC
717 at the maximum recommended human daily dose). In rats, there was a significant increase in the
718 incidence of benign adipose tissue tumors (lipomas) at doses ≥ 0.3 mg/kg/day (approximately
719 2 times human AUC at the maximum recommended human daily dose). These proliferative
720 changes in both species are considered due to the persistent pharmacological overstimulation of
721 adipose tissue.

722 Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial
723 assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in
724 vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about
725 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic
726 activation.

727 Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats
728 given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended
729 human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility
730 (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and
731 estradiol (approximately 20 and 200 times human AUC at the maximum recommended human
732 daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times
733 human AUC at the maximum recommended human daily dose). In juvenile rats dosed from
734 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male
735 reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in
736 females (approximately 68 times human AUC at the maximum recommended human daily
737 dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human
738 AUC at the maximum recommended human daily dose, respectively) diminished the follicular
739 phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge,

740 lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears
741 to be direct inhibition of ovarian steroidogenesis.

742 **13.2 Animal Toxicology**

743 Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs
744 (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at
745 the maximum recommended human daily dose, respectively). Effects in juvenile rats were
746 consistent with those seen in adults. Morphometric measurement indicated that there was
747 hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result
748 of plasma volume expansion.

749 **14 CLINICAL STUDIES**

750 **14.1 Monotherapy**

751 In clinical trials, treatment with AVANDIA resulted in an improvement in glycemic
752 control, as measured by FPG and HbA1c, with a concurrent reduction in insulin and C-peptide.
753 Postprandial glucose and insulin were also reduced. This is consistent with the mechanism of
754 action of AVANDIA as an insulin sensitizer.

755 The maximum recommended daily dose is 8 mg. Dose-ranging trials suggested that no
756 additional benefit was obtained with a total daily dose of 12 mg.

757 Short-Term Clinical Trials: A total of 2,315 patients with type 2 diabetes, previously
758 treated with diet alone or antidiabetic medication(s), were treated with AVANDIA as
759 monotherapy in 6 double-blind trials, which included two 26-week placebo-controlled trials, one
760 52-week glyburide-controlled trial, and 3 placebo-controlled dose-ranging trials of 8 to 12 weeks
761 duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week
762 placebo run-in period prior to randomization.

763 Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes
764 (n = 1,401) with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL
765 [101 to 425 mg/dL] and mean baseline HbA1c 8.9% [5.2% to 16.2%]), were conducted.
766 Treatment with AVANDIA produced statistically significant improvements in FPG and HbA1c
767 compared to baseline and relative to placebo. Data from one of these trials are summarized in
768 Table 11.

769

770 Table 11. Glycemic Parameters in a 26-Week Placebo-Controlled Trial

	Placebo	AVANDIA		AVANDIA	
		4 mg once daily	2 mg twice daily	8 mg once daily	4 mg twice daily
	N = 173	N = 180	N = 186	N = 181	N = 187
FPG (mg/dL)					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference from placebo (adjusted mean)	–	-31 ^a	-43 ^a	-49 ^a	-62 ^a
% of patients with ≥ 30 mg/dL decrease from baseline	19%	45%	54%	58%	70%
HbA1c (%)					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	-0.1	-0.3	-0.7
Difference from placebo (adjusted mean)	–	-0.8 ^a	-0.9 ^a	-1.1 ^a	-1.5 ^a
% of patients with $\geq 0.7\%$ decrease from baseline	9%	28%	29%	39%	54%

771 ^a $P < 0.0001$ compared to placebo.

772
 773 When administered at the same total daily dose, AVANDIA was generally more effective
 774 in reducing FPG and HbA1c when administered in divided doses twice daily compared to once
 775 daily doses. However, for HbA1c, the difference between the 4 mg once daily and 2 mg twice
 776 daily doses was not statistically significant.

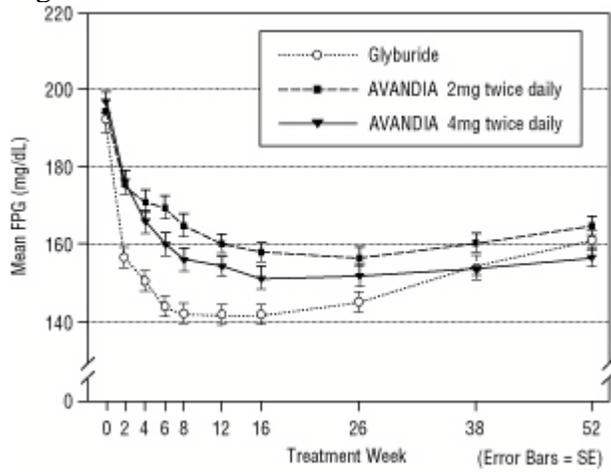
777 **Long-Term Clinical Trials:** Long-term maintenance of effect was evaluated in a
 778 52-week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were
 779 randomized to treatment with AVANDIA 2 mg twice daily (N = 195) or AVANDIA 4 mg twice
 780 daily (N = 189) or glyburide (N = 202) for 52 weeks. Patients receiving glyburide were given an
 781 initial dosage of either 2.5 mg/day or 5.0 mg/day. The dosage was then titrated in 2.5 mg/day
 782 increments over the next 12 weeks, to a maximum dosage of 15.0 mg/day in order to optimize
 783 glycemic control. Thereafter, the glyburide dose was kept constant.

784 The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a
 785 statistically significant improvement in glycemic control from baseline (Figure 3 and Figure 4).
 786 At the end of week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/dL and
 787 -0.53% with AVANDIA 4 mg twice daily; -25.4 mg/dL and -0.27% with AVANDIA 2 mg twice
 788 daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between
 789 AVANDIA 4 mg twice daily and glyburide was not statistically significant at week 52. The
 790 initial fall in FPG with glyburide was greater than with AVANDIA; however, this effect was less
 791 durable over time. The improvement in glycemic control seen with AVANDIA 4 mg twice daily

792 at week 26 was maintained through week 52 of the trial.

793

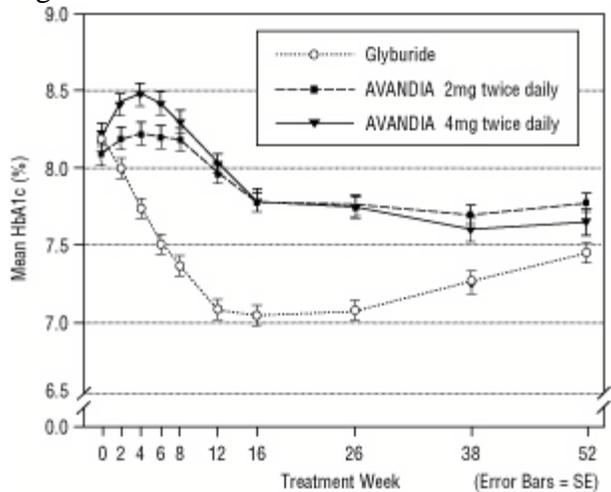
794 Figure 3. Mean FPG Over Time in a 52-Week Glyburide-Controlled Trial



795

796

797 Figure 4. Mean HbA1c Over Time in a 52-Week Glyburide-Controlled Trial



798

799

800 Hypoglycemia was reported in 12.1% of glyburide-treated patients versus 0.5% (2 mg
801 twice daily) and 1.6% (4 mg twice daily) of patients treated with AVANDIA. The improvements
802 in glycemic control were associated with a mean weight gain of 1.75 kg and 2.95 kg for patients
803 treated with 2 mg and 4 mg twice daily of AVANDIA, respectively, versus 1.9 kg in
804 glyburide-treated patients. In patients treated with AVANDIA, C-peptide, insulin, pro-insulin,
805 and pro-insulin split products were significantly reduced in a dose-ordered fashion, compared to
806 an increase in the glyburide-treated patients.

807

808

809

810

A Diabetes Outcome Progression Trial (ADOPT) was a multicenter, double-blind,
controlled trial (N = 4,351) conducted over 4 to 6 years to compare the safety and efficacy of
AVANDIA, metformin, and glyburide monotherapy in patients recently diagnosed with type 2
diabetes mellitus (≤ 3 years) inadequately controlled with diet and exercise. The mean age of

811 patients in this trial was 57 years and the majority of patients (83%) had no known history of
812 cardiovascular disease. The mean baseline FPG and HbA1c were 152 mg/dL and 7.4%,
813 respectively. Patients were randomized to receive either AVANDIA 4 mg once daily, glyburide
814 2.5 mg once daily, or metformin 500 mg once daily, and doses were titrated to optimal glycemic
815 control up to a maximum of 4 mg twice daily for AVANDIA, 7.5 mg twice daily for glyburide,
816 and 1,000 mg twice daily for metformin. The primary efficacy outcome was time to consecutive
817 FPG >180 mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study
818 medication or time to inadequate glycemic control, as determined by an independent
819 adjudication committee.

820 The cumulative incidence of the primary efficacy outcome at 5 years was 15% with
821 AVANDIA, 21% with metformin, and 34% with glyburide (HR 0.68 [95% CI 0.55, 0.85] versus
822 metformin, HR 0.37 [95% CI 0.30, 0.45] versus glyburide).

823 Cardiovascular and adverse event data (including effects on body weight and bone
824 fracture) from ADOPT for AVANDIA, metformin, and glyburide are described in *Warnings and*
825 *Precautions (5.2, 5.5, and 5.8)* and *Adverse Reactions (6.1)*, respectively. As with all
826 medications, efficacy results must be considered together with safety information to assess the
827 potential benefit and risk for an individual patient.

828 **14.2 Combination With Metformin or Sulfonylurea**

829 The addition of AVANDIA to either metformin or sulfonylurea resulted in significant
830 reductions in hyperglycemia compared to either of these agents alone. These results are
831 consistent with an additive effect on glycemic control when AVANDIA is used as combination
832 therapy.

833 Combination With Metformin: A total of 670 patients with type 2 diabetes participated
834 in two 26-week, randomized, double-blind, placebo/active-controlled trials designed to assess the
835 efficacy of AVANDIA in combination with metformin. AVANDIA, administered in either once
836 daily or twice daily dosing regimens, was added to the therapy of patients who were inadequately
837 controlled on a maximum dose (2.5 grams/day) of metformin.

838 In one trial, patients inadequately controlled on 2.5 grams/day of metformin (mean
839 baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive 4 mg of
840 AVANDIA once daily, 8 mg of AVANDIA once daily, or placebo in addition to metformin. A
841 statistically significant improvement in FPG and HbA1c was observed in patients treated with
842 the combinations of metformin and 4 mg of AVANDIA once daily and 8 mg of AVANDIA once
843 daily, versus patients continued on metformin alone (Table 12).

844

845 Table 12. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus
 846 Metformin

	Metformin	AVANDIA 4 mg once daily + metformin	AVANDIA 8 mg once daily + metformin
	N = 113	N = 116	N = 110
FPG (mg/dL)			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	-33	-48
Difference from metformin alone (adjusted mean)	–	-40 ^a	-53 ^a
% of patients with ≥30 mg/dL decrease from baseline	20%	45%	61%
HbA1c (%)			
Baseline (mean)	8.6	8.9	8.9
Change from baseline (mean)	0.5	-0.6	-0.8
Difference from metformin alone (adjusted mean)	–	-1.0 ^a	-1.2 ^a
% of patients with ≥0.7% decrease from baseline	11%	45%	52%

847 ^a P <0.0001 compared to metformin.
 848

849 In a second 26-week trial, patients with type 2 diabetes inadequately controlled on
 850 2.5 grams/day of metformin who were randomized to receive the combination of AVANDIA
 851 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in
 852 glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect
 853 for HbA1c of -0.8% over metformin alone. The combination of metformin and AVANDIA
 854 resulted in lower levels of FPG and HbA1c than either agent alone.

855 Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of
 856 metformin and who were switched to monotherapy with AVANDIA demonstrated loss of
 857 glycemic control, as evidenced by increases in FPG and HbA1c. In this group, increases in LDL
 858 and VLDL were also seen.

859 **Combination With a Sulfonylurea:** A total of 3,457 patients with type 2 diabetes
 860 participated in ten 24- to 26-week randomized, double-blind, placebo/active-controlled trials and
 861 one 2-year double-blind, active-controlled trial in elderly patients designed to assess the efficacy
 862 and safety of AVANDIA in combination with a sulfonylurea. AVANDIA 2 mg, 4 mg, or 8 mg
 863 daily was administered, either once daily (3 trials) or in divided doses twice daily (7 trials), to
 864 patients inadequately controlled on a submaximal or maximal dose of sulfonylurea.

865 In these trials, the combination of AVANDIA 4 mg or 8 mg daily (administered as single
 866 or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared

867 to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 13 shows pooled
868 data for 8 trials in which AVANDIA added to sulfonylurea was compared to placebo plus
869 sulfonylurea.
870

871 Table 13. Glycemic Parameters in 24- to 26-Week Combination Trials of AVANDIA Plus
 872 Sulfonylurea

Twice Daily Divided Dosing (5 Trials)	Sulfonylurea	AVANDIA 2 mg twice daily + sulfonylurea	Sulfonylurea	AVANDIA 4 mg twice daily + sulfonylurea
	N = 397	N = 497	N = 248	N = 346
FPG (mg/dL)				
Baseline (mean)	204	198	188	187
Change from baseline (mean)	11	-29	8	-43
Difference from sulfonylurea alone (adjusted mean)	–	-42 ^a	–	-53 ^a
% of patients with ≥30 mg/dL decrease from baseline	17%	49%	15%	61%
HbA1c (%)				
Baseline (mean)	9.4	9.5	9.3	9.6
Change from baseline (mean)	0.2	-1.0	0.0	-1.6
Difference from sulfonylurea alone (adjusted mean)	–	-1.1 ^a	–	-1.4 ^a
% of patients with ≥0.7% decrease from baseline	21%	60%	23%	75%
Once Daily Dosing (3 Trials)		AVANDIA 4 mg once daily + sulfonylurea	Sulfonylurea	AVANDIA 8 mg once daily + sulfonylurea
	N = 172	N = 172	N = 173	N = 176
FPG (mg/dL)				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	–	-47 ^a	–	-66 ^a
% of patients with ≥30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline (mean)	0.4	-0.5	0.1	-1.2
Difference from sulfonylurea alone (adjusted mean)	–	-0.9 ^a	–	-1.4 ^a
% of patients with ≥0.7% decrease from baseline	11%	36%	20%	68%

873 ^a P <0.0001 compared to sulfonylurea alone.

874

875 One of the 24- to 26-week trials included patients who were inadequately controlled on
876 maximal doses of glyburide and switched to 4 mg of AVANDIA daily as monotherapy; in this
877 group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.

878 In a 2-year double-blind trial, elderly patients (aged 59 to 89 years) on half-maximal
879 sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of AVANDIA
880 (n = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (n = 110),
881 to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and
882 7.72%, respectively, for the AVANDIA plus glipizide arm and 159 mg/dL and 7.65%,
883 respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG \geq 180 mg/dL)
884 occurred in a significantly lower proportion of patients (2%) on AVANDIA plus glipizide
885 compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on
886 combination therapy completed the 2 years of therapy while only 51% completed on glipizide
887 monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year
888 trial period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for
889 HbA1c compared to no change on the glipizide arm.

890 **14.3 Combination With Sulfonylurea Plus Metformin**

891 In two 24- to 26-week, double-blind, placebo-controlled, trials designed to assess the
892 efficacy and safety of AVANDIA in combination with sulfonylurea plus metformin, AVANDIA
893 4 mg or 8 mg daily, was administered in divided doses twice daily, to patients inadequately
894 controlled on submaximal (10 mg) and maximal (20 mg) doses of glyburide and maximal dose
895 of metformin (2 g/day). A statistically significant improvement in FPG and HbA1c was observed
896 in patients treated with the combinations of sulfonylurea plus metformin and 4 mg of AVANDIA
897 and 8 mg of AVANDIA versus patients continued on sulfonylurea plus metformin, as shown in
898 Table 14.

899

900 Table 14. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus
 901 Sulfonylurea and Metformin

	Sulfonylurea + metformin	AVANDIA 2 mg twice daily + sulfonylurea + metformin	AVANDIA 4 mg twice daily + sulfonylurea + metformin
	N = 273	N = 276	N = 277
FPG (mg/dL)			
Baseline (mean)	189	190	192
Change from baseline (mean)	14	-19	-40
Difference from sulfonylurea plus metformin (adjusted mean)	–	-30 ^a	-52 ^a
% of patients with ≥30 mg/dL decrease from baseline	16%	46%	62%
HbA1c (%)			
Baseline (mean)	8.7	8.6	8.7
Change from baseline (mean)	0.2	-0.4	-0.9
Difference from sulfonylurea plus metformin (adjusted mean)	–	-0.6 ^a	-1.1 ^a
% of patients with ≥0.7% decrease from baseline	16%	39%	63%

902 ^a P <0.0001 compared to placebo.
 903

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935 **16 HOW SUPPLIED/STORAGE AND HANDLING**

936 Each pentagonal film-coated TILTAB tablet contains rosiglitazone as the maleate as
937 follows: 2 mg–pink, debossed with SB on one side and 2 on the other; 4 mg–orange, debossed
938 with SB on one side and 4 on the other; 8 mg–red-brown, debossed with SB on one side and 8 on
939 the other.

940 2 mg bottles of 60: NDC 0173-0834-18

941 4 mg bottles of 30: NDC 0173-0835-13

942 8 mg bottles of 30: NDC 0173-0836-13

943 Store at 25°C (77°F); excursions 15° to 30°C (59° to 86°F). Dispense in a tight, light-
944 resistant container.

945 **17 PATIENT COUNSELING INFORMATION**

946 See Medication Guide.

947 **17.1 Patient Advice**

948 There are multiple medications available to treat type 2 diabetes. The benefits and risks
949 of each available diabetes medication should be taken into account when choosing a particular
950 diabetes medication for a given patient.

951 Patients should be informed of the risks and benefits of AVANDIA. AVANDIA should
952 only be taken by adults with type 2 diabetes who are already taking AVANDIA, or who are not
953 already taking AVANDIA and are unable to achieve adequate glycemic control on other diabetes
954 medications, and, in consultation with their healthcare provider, have decided not to take
955 pioglitazone (ACTOS) for medical reasons. Inform patients that they must be enrolled in the
956 AVANDIA-Rosiglitazone Medicines Access Program in order to receive AVANDIA.

- 957 Patients should be informed of the following:
- 958 • AVANDIA is not recommended for patients with symptomatic heart failure.
 - 959 • Results of a set of clinical trials suggest that treatment with AVANDIA is associated with an
960 increased risk for myocardial infarction (heart attack), especially in patients taking insulin.
961 Clinical trials have not shown any difference between AVANDIA and comparator
962 medications in overall mortality or CV-related mortality.
 - 963 • AVANDIA is not recommended for patients who are taking insulin.
 - 964 • Management of type 2 diabetes should include diet control. Caloric restriction, weight loss,
965 and exercise are essential for the proper treatment of the diabetic patient because they help
966 improve insulin sensitivity. This is important not only in the primary treatment of type 2
967 diabetes, but in maintaining the efficacy of drug therapy.
 - 968 • It is important to adhere to dietary instructions and to regularly have blood glucose and
969 glycosylated hemoglobin tested. It can take 2 weeks to see a reduction in blood glucose and 2
970 to 3 months to see the full effect of AVANDIA.
 - 971 • Blood will be drawn to check their liver function prior to the start of therapy and periodically
972 thereafter per the clinical judgment of the healthcare professional. Patients with unexplained
973 symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should
974 immediately report these symptoms to their physician.
 - 975 • Patients who experience an unusually rapid increase in weight or edema or who develop
976 shortness of breath or other symptoms of heart failure while on AVANDIA should
977 immediately report these symptoms to their physician.
 - 978 • AVANDIA can be taken with or without meals.
 - 979 • When using AVANDIA in combination with other hypoglycemic agents, the risk of
980 hypoglycemia, its symptoms and treatment, and conditions that predispose to its development
981 should be explained to patients and their family members.
 - 982 • Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some
983 premenopausal anovulatory women. As a result, these patients may be at an increased risk for
984 pregnancy while taking AVANDIA. Thus, adequate contraception in premenopausal women
985 should be recommended. This possible effect has not been specifically investigated in
986 clinical trials so the frequency of this occurrence is not known.

987
988 AVANDIA and TILTAB are registered trademarks of GlaxoSmithKline. ACTOS is a registered
989 trademark of Takeda Pharmaceutical Company Limited.

990



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992 GlaxoSmithKline
993 Research Triangle Park, NC 27709
994

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997 Month 2011

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MEDICATION GUIDE
AVANDIA® (ah-VAN-dee-a)
(rosiglitazone maleate) Tablets

1003 Read this Medication Guide carefully before you start taking AVANDIA and each
1004 time you get a refill. There may be new information. This information does not take
1005 the place of talking with your doctor about your medical condition or your
1006 treatment. If you have any questions about AVANDIA, ask your doctor or
1007 pharmacist.

1008
1009 **What is the most important information I should know about AVANDIA?**

1010
1011 AVANDIA is available only through the AVANDIA-Rosiglitazone Medicines Access
1012 Program. Both you and your doctor must be enrolled in the program so that you
1013 can get AVANDIA. To enroll, you must:

- 1014
- 1015 • talk to your doctor,
 - 1016 • understand the risks and benefits of AVANDIA, and
 - 1017 • agree to enroll in the program.

1018 **AVANDIA may cause serious side effects, including:**

1019
1020 **New or worse heart failure**

- 1021
- 1022 • AVANDIA can cause your body to keep extra fluid (fluid retention), which leads
1023 to swelling (edema) and weight gain. Extra body fluid can make some heart
1024 problems worse or lead to heart failure. Heart failure means your heart does not
1025 pump blood well enough.
 - 1026 • If you have severe heart failure, you cannot start AVANDIA.
 - 1027 • If you have heart failure with symptoms (such as shortness of breath or
1028 swelling), even if these symptoms are not severe, AVANDIA may not be right for
1029 you.

1030 Call your doctor right away if you have any of the following:

- 1031
- 1032 • swelling or fluid retention, especially in the ankles or legs
 - 1033 • shortness of breath or trouble breathing, especially when you lie down
 - 1034 • an unusually fast increase in weight
 - 1035 • unusual tiredness

1036 **Myocardial Infarction (“Heart Attack”)**

1037 AVANDIA may raise the risk of a heart attack. The risk of having a heart attack may
1038 be higher in people who take AVANDIA with insulin. Most people who take insulin

1039 should not also take AVANDIA.

1040 **Symptoms of a heart attack can include the following:**

- 1041 • chest discomfort in the center of your chest that lasts for more than a few
- 1042 minutes, or that goes away or comes back
- 1043 • chest discomfort that feels like uncomfortable pressure, squeezing, fullness or
- 1044 pain
- 1045 • pain or discomfort in your arms, back, neck, jaw or stomach
- 1046 • shortness of breath with or without chest discomfort
- 1047 • breaking out in a cold sweat
- 1048 • nausea or vomiting
- 1049 • feeling lightheaded

1050 **Call your doctor or go to the nearest hospital emergency room right away if**

1051 **you think you are having a heart attack.**

1052

1053 People with diabetes have a greater risk for heart problems. It is important to work

1054 with your doctor to manage other conditions, such as high blood pressure or high

1055 cholesterol.

1056

1057 AVANDIA can have other serious side effects. Be sure to read the section below

1058 “What are possible side effects of AVANDIA?”.

1059

1060 **What is AVANDIA?**

1061 AVANDIA is a prescription medicine used with diet and exercise to treat certain

1062 adults with type 2 (“adult-onset” or “non-insulin dependent”) diabetes mellitus

1063 (“high blood sugar”) who are:

- 1064 • already taking AVANDIA or
- 1065 • unable to control their blood sugar on other diabetes medicines, and after
- 1066 talking with their doctor have decided not to take pioglitazone (ACTOS)

1067

1068 AVANDIA helps to control high blood sugar. AVANDIA may be used alone or with

1069 other diabetes medicines. AVANDIA can help your body respond better to insulin

1070 made in your body. AVANDIA does not cause your body to make more insulin.

1071

1072 AVANDIA is not for people with type 1 diabetes mellitus or to treat a condition

1073 called diabetic ketoacidosis.

1074

1075 It is not known if AVANDIA is safe and effective in children under 18 years old.

1076

1077 **Who should not take AVANDIA?**

1078 Many people with heart failure should not start taking AVANDIA. See “What should

1079 I tell my doctor before taking AVANDIA?”.

1080

1081 **What should I tell my doctor before taking AVANDIA?**

1082 Before starting AVANDIA, ask your doctor about what the choices are for diabetes
1083 medicines, and what the expected benefits and possible risks are for you in
1084 particular.

1085

1086 Before taking AVANDIA, tell your doctor about all your medical conditions, including
1087 if you:

1088 • **have heart problems or heart failure.**

1089 • **have type 1 (“juvenile”) diabetes or had diabetic ketoacidosis.** These
1090 conditions should be treated with insulin.

1091 • **have a type of diabetic eye disease called macular edema** (swelling of the
1092 back of the eye).

1093 • **have liver problems.** Your doctor should do blood tests to check your liver
1094 before you start taking AVANDIA and during treatment as needed.

1095 • **had liver problems while taking REZULIN® (troglitazone), another
1096 medicine for diabetes.**

1097 • **are pregnant or plan to become pregnant.** AVANDIA should not be used
1098 during pregnancy. It is not known if AVANDIA can harm your unborn baby. You
1099 and your doctor should talk about the best way to control your diabetes during
1100 pregnancy. If you are a premenopausal woman (before the “change of life”) who
1101 does not have regular monthly periods, AVANDIA may increase your chances of
1102 becoming pregnant. Talk to your doctor about birth control choices while taking
1103 AVANDIA. Tell your doctor right away if you become pregnant while taking
1104 AVANDIA.

1105 • **are breast-feeding or planning to breast-feed.** It is not known if AVANDIA
1106 passes into breast milk. You should not use AVANDIA while breast-feeding.

1107

1108 Tell your doctor about all the medicines you take including prescription and non-
1109 prescription medicines, vitamins or herbal supplements. AVANDIA and certain other
1110 medicines can affect each other and may lead to serious side effects including high
1111 or low blood sugar, or heart problems. Especially tell your doctor if you take:

1112 • **insulin.**

1113 • **any medicines for high blood pressure, high cholesterol or heart failure,
1114 or for prevention of heart disease or stroke.**

1115

1116 Know the medicines you take. Keep a list of your medicines and show it to your
1117 doctor and pharmacist before you start a new medicine. They will tell you if it is
1118 alright to take AVANDIA with other medicines.

1119

1120 **How should I take AVANDIA?**

- 1121 • Take AVANDIA exactly as prescribed. Your doctor will tell you how many tablets
1122 to take and how often. The usual daily starting dose is 4 mg a day taken one
1123 time each day or 2 mg taken two times each day. Your doctor may need to
1124 adjust your dose until your blood sugar is better controlled.
- 1125 • AVANDIA may be prescribed alone or with other diabetes medicines. This will
1126 depend on how well your blood sugar is controlled.
- 1127 • Take AVANDIA with or without food.
- 1128 • It can take 2 weeks for AVANDIA to start lowering blood sugar. It may take 2 to
1129 3 months to see the full effect on your blood sugar level.
- 1130 • If you miss a dose of AVANDIA, take it as soon as you remember, unless it is
1131 time to take your next dose. Take your next dose at the usual time. Do not take
1132 double doses to make up for a missed dose.
- 1133 • If you take too much AVANDIA, call your doctor or poison control center right
1134 away.
- 1135 • Test your blood sugar regularly as your doctor tells you.
- 1136 • Diet and exercise can help your body use its blood sugar better. It is important
1137 to stay on your recommended diet, lose extra weight, and get regular exercise
1138 while taking AVANDIA.
- 1139 • Your doctor should do blood tests to check your liver before you start AVANDIA
1140 and during treatment as needed. Your doctor should also do regular blood sugar
1141 tests (for example, "A1C") to monitor your response to AVANDIA.

1142

1143 **What are possible side effects of AVANDIA?**

1144 **AVANDIA may cause serious side effects including:**

- 1145 • **New or worse heart failure.** See "What is the most important information I
1146 should know about AVANDIA?".
- 1147 • **Heart attack.** See "What is the most important information I should know
1148 about AVANDIA?".
- 1149 • **Swelling (edema).** AVANDIA can cause swelling due to fluid retention. See
1150 "What is the most important information I should know about AVANDIA?".
- 1151 • **Weight gain.** AVANDIA can cause weight gain that may be due to fluid
1152 retention or extra body fat. Weight gain can be a serious problem for people
1153 with certain conditions including heart problems. See "What is the most
1154 important information I should know about AVANDIA?".
- 1155 • **Liver problems.** It is important for your liver to be working normally when you
1156 take AVANDIA. Your doctor should do blood tests to check your liver before you
1157 start taking AVANDIA and during treatment as needed. Call your doctor right
1158 away if you have unexplained symptoms such as:

- 1159 • nausea or vomiting
- 1160 • stomach pain
- 1161 • unusual or unexplained tiredness
- 1162 • loss of appetite
- 1163 • dark urine
- 1164 • yellowing of your skin or the whites of your eyes.
- 1165 • **Macular edema** (a diabetic eye disease with swelling in the back of the eye).
1166 Tell your doctor right away if you have any changes in your vision. Your doctor
1167 should check your eyes regularly. Very rarely, some people have had vision
1168 changes due to swelling in the back of the eye while taking AVANDIA.
- 1169 • **Fractures (broken bones)**, usually in the hand, upper arm or foot. Talk to
1170 your doctor for advice on how to keep your bones healthy.
- 1171 • **Low red blood cell count (anemia)**.
- 1172 • **Low blood sugar (hypoglycemia)**. Lightheadedness, dizziness, shakiness or
1173 hunger may mean that your blood sugar is too low. This can happen if you skip
1174 meals, if you use another medicine that lowers blood sugar, or if you have
1175 certain medical problems. Call your doctor if low blood sugar levels are a
1176 problem for you.
- 1177 • **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy.
1178 Ovulation may happen in premenopausal women who do not have regular
1179 monthly periods. This can increase the chance of pregnancy. See “What should I
1180 tell my doctor before taking AVANDIA?”.

1181
1182 The most common side effects of AVANDIA reported in clinical trials included cold-
1183 like symptoms and headache.

1184
1185 Call your doctor for medical advice about side effects. You may report side effects
1186 to FDA at 1-800-FDA-1088.

1187
1188 **How should I store AVANDIA?**

- 1189 • Store AVANDIA at room temperature, 59° to 86°F (15° to 30°C). Keep AVANDIA
1190 in the container it comes in.
- 1191 • Safely, throw away AVANDIA that is out of date or no longer needed.
- 1192 • Keep AVANDIA and all medicines out of the reach of children.

1193
1194 **General information about AVANDIA**

1195 Medicines are sometimes prescribed for purposes other than those listed in a
1196 Medication Guide. Do not use AVANDIA for a condition for which it was not
1197 prescribed. Do not give AVANDIA to other people, even if they have the same
1198 symptoms you have. It may harm them.

1199
1200 This Medication Guide summarizes important information about AVANDIA. If you
1201 would like more information, talk with your doctor. You can ask your doctor or
1202 pharmacist for information about AVANDIA that is written for healthcare
1203 professionals. You can also find out more about AVANDIA by calling 1-888-825-
1204 5249.

1205
1206 **What are the ingredients in AVANDIA?**

1207 Active Ingredient: Rosiglitazone maleate.

1208 Inactive Ingredients: Hypromellose 2910, lactose monohydrate, magnesium
1209 stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch
1210 glycolate, titanium dioxide, triacetin, and 1 or more of the following: Synthetic red
1211 and yellow iron oxides and talc.

1212
1213 Always check to make sure that the medicine you are taking is the correct one.
1214 AVANDIA tablets are triangles with rounded corners and look like this:

1215 2 mg – pink with "SB" on one side and "2" on the other.

1216 4 mg – orange with "SB" on one side and "4" on the other.

1217 8 mg – red-brown with "SB" on one side and "8" on the other.

1218
1219 AVANDIA is a registered trademark of GlaxoSmithKline.

1220 The other brands listed are trademarks of their respective owners and are not
1221 trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with
1222 and do not endorse GlaxoSmithKline or its products.

1223
1224 **This Medication Guide has been approved by the U.S. Food and Drug**
1225 **Administration.**

1226



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1233 Month 2011

1234 AVD: XMG